REMARKS

The Official Action dated February 19, 2004 has been carefully considered. Accordingly, the changes presented herewith, taken with the following remarks, are believed sufficient to place the present application in condition for allowance. Reconsideration is respectfully requested.

By the present Amendment, claims 8, 11-13 and 19-23 have been amended to respond to the new rejections under 35 U.S.C. §112 set forth in the Official Action. It is believed that these changes do not involve any introduction of new matter, and do not raise any new issues subsequent to final rejection, whereby entry is believed to be in order and is respectfully requested.

Claims 8-13, 17, 18, 22 and 23 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner asserted that it is unclear how the membrane or flow matrix has been "adapted" to chromatographically separate each of the two components from one another and from the sample.

This rejection is traversed. However, to expedite prosecution, claims 8 and 11-13 have been revised to recite that the flow matrix contains ion exchange functions sufficient to chromatographically separate at least two components from the sample and from one another during their transport along the lateral flow matrix. The term "adapted" questioned by the Examiner has been omitted from these claims. It is therefore submitted that claims 8-13, 17, 18, 22 and 23 are definite in accordance with the requirements of 35 U.S.C. §112, second paragraph, whereby the rejection has been overcome. Reconsideration is respectfully requested.

Claims 19-23 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner asserted that these claims do

not have support in the specification as originally filed as the specification only describes proteins with different isoelectric points and is silent on other components such as peptides, nucleic acids and polynucleotides having different isoelectric points.

This rejection is traversed. However, to expedite prosecution, claims 19-23 have been amended to clarify that the proteins have different isoelectric points. It is therefore submitted that the specification describes the invention as claimed in accordance with the requirements of 35 U.S.C. §112, first paragraph, whereby the rejection has been overcome. Reconsideration is respectfully requested.

Claims 1-23 were rejected under 35 U.S.C. §103(a) as being unpatentable over the Pristoupil publication entitled "Microchromatography and Microelectrophoresis on Nitrocellulose Membranes," *Chromatography Review*, 12:109-125 (1970). The Examiner asserted that Pristoupil teaches the use of nitrocellulose membrane in chromatography and electrophoresis separation of proteins and nucleic acid. The Examiner further asserted that Pristoupil teaches that the membrane is laid flat on a glass plate in a chromatography chamber and although Pristoupil does not specifically recite a membrane comprising the ion-exchange functional groups of claims 1 and 8, Pristoupil teaches a membrane having ion-exchange function and it would be routine experimentation for one of ordinary skill in the art to employ the claimed groups. In response to Applicants' previous arguments, the Examiner asserted that the functional action of the ion-exchange groups have not been properly recited and although Applicants appear to argue that the ion-exchange groups bind the proteins and aid in their separation, such is not recited in the claims.

At page 6 of the Official Action, the Examiner responded to Applicants' previous argument that Pristoupil et al do not teach separation of each of two components from each other and from the sample. The Examiner asserted that the paragraph bridging pages 116 and

117 teaches ion exchange function and ionic attractions between proteins of different isoelectric points in the membrane and the paragraph bridging pages 120 and 121 teaches fractionation of human serum into 8-10 zones. Finally, the Examiner referred to page 121, paragraph 5, as teaching separation of eight ethanol-soluble dyes into individual components.

However, as set forth in detail below, Applicants submit that the chromatographic assay methods defined by claims 1-7, 11, 12, 14-16 and 19-21 and the chromatographic devices defined by claims 8-10, 13, 17, 18, 22 and 23 are nonobvious over and patentably distinguishable from Pristoupil. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

More particularly, claims 1, 11 and 12 are directed to a chromatographic assay method which comprises providing a polymeric membrane type flow matrix attached to a liquid impervious backing, which flow matrix permits a capillary force assisted lateral flow therethrough and is treated to reduce or eliminate non-specific adsorption properties of the flow matrix, applying to the flow matrix a sample containing at least two components, initiating a first lateral flow of aqueous fluid to transport the sample through the flow matrix and chromatographically separate each of the two components from one another from the sample as they flow along the lateral flow matrix, interrupting the lateral flow, and detecting at least one of the separated components according to specified procedures. According to claims 8 and 13, the chromatographic device comprises a polymeric membrane type flow matrix attached to a liquid-impervious backing, which membrane permits a capillary force assisted lateral flow therethrough and contains ion exchange functional groups. The flow matrix is adapted to chromatographically separate each of at least two components from one another and from a sample containing the components as they flow along the lateral flow matrix.

Claims 1 and 8 both recite that the flow matrix is a porous polymer material with pores in the range of 0.01-20 μm and that the ion-exchange functional groups are selected from the group consisting of diethyl aminoethyl (DEAE), trimethyl hydroxypropyl (QA), quaternary aminoethyl (QAE), quaternary aminomethyl (Q), diethyl-(2-hydroxypropyl)-aminoethyl, triethyl aminomethyl (TEAE), triethylaminopropyl (TEAP), polyethyleneimine (PEI), methacrylate, carboxymethyl (CM), orthophosphate (P), sulfonate (S), sulfoethyl (SE) and sulfopropyl (SP) groups.

As set forth in the present specification, for example at page 2, beginning at line 17, it has surprisingly been found that the chromatographic separation employing a flow matrix as defined in claims 1, 8 and 11-13 and containing ion-exchange functional groups provides a simple, fast and inexpensive analytical method for separation of biomolecules in complex mixtures. The chromatographic separation is facilitated by the ion-exchange functional groups. As described in the example set forth at pages 9-12, the methods and devices are therefore particularly suitable for separation of proteins, peptides, nucleic acids or polynucleotides.

In contrast to the presently claimed methods and devices which employ ion-exchange functional groups in chromatography, Pristoupil discloses adsorption chromatography and hydrophobic interaction chromatography, and discloses electrophoresis techniques. However, Pristoupil provides no teaching or suggestion relating to the use of ion exchange functional groups to obtain chromatographic separation of components. Pristoupil mentions ion-exchange capacity only once at page 115 relative to the titration of the ion-exchange capacity of nitrocellulose membranes. The titration indicated the nitrocellulose membranes had an ion-exchange capacity of about 0.1 mequiv. NaOh/g, which Pristoupil indicates is "rather low" and corresponds approximately to the capacity of ordinary filter paper.

One of ordinary skill in the art will recognize that ion-exchange capacity is an inherent property of any charged chemical entity, even of those quite unsuitable for ion-exchange applications, such as filter paper. The only teaching by Pristoupil relating to ion-exchange therefore is to confirm that nitrocellulose membranes, like ordinary filter paper, are not considered by those of ordinary skill in the art to serve as ion-exchange-functional materials. Importantly, Pristoupil does not correlate any ion-exchange capacity to any ion-exchange function, and particularly, Pristoupil provides no teaching or suggestion for using ion-exchange functionality in chromatography. Rather, Pristoupil concentrates on adsorption chromatography in the subsequent paragraphs of page 115 and page 116.

Differences between ion-exchange and adsorption chromatography are apparent in the *Steadman's Medical Dictionary*, previously cited by the Examiner, which discloses adsorption chromatography is based on separation achieved by the difference in degree of adsorption of compounds to a stationary phase, while ion-exchange chromatography is based on separation of substances by electrostatic interactions with the stationary phase. One skilled in the art will therefore appreciate the teachings of Pristoupil relating to adsorption chromatography do not teach or suggest the application of ion-exchange functionality to obtain chromatographic separation in a lateral flow matrix according to the presently claimed methods and devices. In fact, as the present methods and devices employ the addition of external ion-exchange groups and a treatment for reducing or eliminating non-specific adsorption properties of the flow matrix, the present methods and devices clearly distinguish and differentiate from the adsorption chromatography techniques of Pristoupil.

In the rejection, the Examiner asserts that the prior art teaches that nitrocellulose membranes may be impregnated with various ion-exchange functional groups and often vary according to the sample being analyzed in the assay conditions. However, Applicants find no

such teaching by Pristoupil or otherwise in the cited prior art and request that the Examiner indicate where in the record these asserted prior art teachings are found.

In the Official Action, the Examiner asserted that the paragraph bridging pages 116 and 117 of Pristoupil teaches ion-exchange function and ionic attractions between proteins of different isoelectric points in a membrane. However, in the paragraph bridging pages 116-117, Pristoupil is discussing the adsorption of the high molecular weight proteins as described at pages 114-115, as contrasted with the migration of peptides, amino acids and other lower-molecular substances of hydrophilic character, also described at pages 114-115. Thus, the discussion at pages 116-117 does not provide any further relevant teaching, and particularly does not teach or suggest chromatographic separation of two or more components by ion-exchange chromatography. This is particularly apparent in view of the discussion at page 115 recognizing that the ion-exchange capacity of the nitrocellulose membranes was "rather low" and corresponded approximately to the capacity of ordinary filter paper.

The Examiner also asserted in the Official Action that the paragraph bridging pages 120 and 121 of Pristoupil teaches fractionation of human serum into 8-10 zones and that page 121, paragraph 5 of Pristoupil teaches separation of eight ethanol-soluble dyes into individual components. However, at pages 120-121, the reference to fractionation of human serum into 8-10 zones refers to the results of microelectrophoresis, particularly on a membrane impregnated with neutral detergents (Tweens), and is not the result of any ion-exchange chromatography method. In the fifth paragraph on page 121, reference is made to a simple separation of binary mixtures of various types of nucleic acids or proteins when chromatography, electrophoresis or both techniques are used as described in Table 2. A review of Table 2 indicates that the substances to be separated merely constituted substances quoted on the left hand side in the first column as remaining at the start or in its vicinity and

the other substances migrating without any significant adsorption. One of ordinary skill in the art will recognize that this is not chromatography as presently claimed. The conclusions of Pristoupil at page 123 merely acknowledge adsorption of proteins versus non-adsorption of low-molecular substances on intact nitrocellulose membranes and the use of electrophoresis for separation of proteins. In fact, these conclusions highlight the failure of Pristoupil to teach or suggest the use of ion-exchange chromatography as presently claimed for chromatographic separation of components.

Finally, with respect to the dye separation shown in Fig. 10 at page 122 and described at page 123 of Pristoupil, there is no teaching or suggestion that the nitrocellulose membrane employed therein contains ion-exchange functional groups as required by the present claims. Moreover, one of ordinary skill in the art will recognize that the dye separation disclosed by Pristoupil was conducted in apolar solvent, namely ethanol-chlorform, ethanol-chlorform-acidic acid and ethanol-25% ammonia, and that it is impossible to effectively use such apolar solvents in ion-exchange chromatography.

Importantly, the chromatography method taught by Pristoupil adsorbs high molecular weight proteins of all types upon sample application as set forth in Fig. 3d at page 114. Pristoupil further discloses that low molecular weight components separate as a group to the front of a developing solution, as also shown in Fig. 3d at page 114.

In contrast, the chromatographic assay methods of claims 1, 11 and 12 require chromatographic separation of each of two components from one another and from the sample as they flow along the lateral flow matrix. As discussed above, the separation is achieved as the ion exchange functional groups allow separation of the individual components based on electrostatic interaction with the flow matrix containing ion-exchange functional groups. Thus, rather than separating high molecular weight proteins as a group by

initial adsorpotion and low molecular weight components as a group at the front of a developing solution, the present methods provide separation of individual components. One skilled in the art will recognize therefore that the present methods provide a significant advantage over the non-specific techniques generally disclosed by Pristoupil.

Similarly, the chromatographic devices defined by claims 8 and 13 require a polymeric membrane containing ion-exchange functional groups sufficient to chromatographically separate each of at least two components from one another and from the sample containing the components as they flow along the lateral flow matrix. As the device disclosed by Pristoupil only adsorbs high molecular weight proteins as a group and separates low molecular substances at the front of the developing solution, again as a group, Pristoupil does not teach or suggest a chromatographic device as presently claimed.

Thus, not only does Pristoupil not teach or suggest a flow matrix containing ion-exchange functional groups as recited in claims 1, 8 and 11-13, Pristoupil provides no teaching or suggestion regarding the separation of individual components by use of ion-exchange functional groups in a flow matrix. To the contrary, Pristoupil, at best, discloses adsorption of high molecular weight proteins as a group and separation of low molecular weight components as a group at the front of a developing solution.

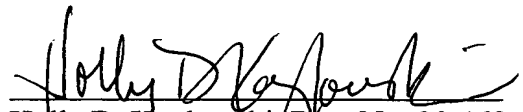
The Examiner asserts that Pristoupil could be modified through routine experimentation to result in the claimed invention. However, there is no evidence of record to support the Examiner's assertion, and the specific separation of components as presently claimed, undisclosed by Pristoupil, rebuts the Examiner's assertion. Moroever, the mere fact that prior art could be modified to result in a claimed invention would not have made the modification obvious unless the prior art suggested the desirability of the modification, *In re Mills*, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). Pristoupil provides no suggestion for modifying

the technique disclosed therein in order to arrive at either the presently claimed chromatographic assay methods or the presently claimed chromatographic devices, regardless of the specific ion-exchange groups employed therein. Thus, Pristoupil does not render the presently claimed methods and devices obvious under 35 U.S.C. §103. It is therefore submitted that the methods and devices defined by claims 1-23 are nonobvious over and patentably distinguishable from Pristoupil, whereby the rejection under 35 U.S.C. §103 has been overcome. Reconsideration is respectfully requested.

Finally, Applicants' undersigned representative wishes to note that several telephone calls were made to the Examiner in an attempt to arrange an interview to discuss the amendments and arguments presented herein. However, the Examiner would not consent to an interview to discuss these matters.

It is believed that the above represents a complete response to the rejections set forth in the Official Action, and places the present application in condition for allowance. In the event that the present Amendment does not place this application in condition for allowance, entry of this Amendment for purposes of appeal is requested. Reconsideration and an early allowance are requested.

Respectfully submitted,



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